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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C08J 3/075, A61K 47/42

A1

(11) International Publication Number: WO 97/39050

(43) International Publication Date: 23 October 1997 (23.10.97)

(21) International Application Number: PCT/US97/06816

(22) International Filing Date: 18 April 1997 (18.04.97)

(30) Priority Data:
08/634,295 18 April 1996 (18.04.96) US

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: SUSTAINED RELEASE HETERODISPERSE HYDROGEL SYSTEMS - AMORPHOUS DRUGS

(57) Abstract

Sustained release oral solid dosage forms comprising agglomerated particles of a therapeutically active medicament in amorphous form, a gelling agent, an ionizable gel strength enhancing agent and an inert diluent, as well as processes for preparing and using the same are disclosed. The sustained release oral solid dosage forms are useful in the treatment of hypertension in human patients.

increases the gel strength of the gel matrix, and from about 0 to about 89% by weight of an inert pharmaceutical diluent; adding an effective amount of a medicament having a solubility of less than about 10 g/l to render a desired therapeutic effect, and thereafter tableting the resulting mixture such that a product is obtained having a ratio of medicament to gelling agent from about 1:3 to about 1:8. The resulting tablet provides therapeutically effective blood levels of the medicament for at least about 12 hours, and preferably about 24 hours. A gel matrix is created by exposure of the gelling agent to an environmental fluid (e.g., gastrointestinal fluid or an in-vitro dissolution bath).

The present invention is further related to a sustained release oral solid dosage form for absorption of a therapeutically active medicament in the gastrointestinal tract, comprising an agglomerated particle. The agglomerated particle includes a medicament and a sustained release excipient. The sustained release excipient is comprised of a gelling agent that is in turn comprised of xanthan gum and locusts bean gum, providing a controlled release gel when exposed to environmental fluids according to the invention. The sustained release excipient also preferably includes an inert pharmaceutical diluent, the ratio of the inert diluent to said gelling agent being from about 1:8 to about 8:1.

In preferred embodiments, the ratio of the xanthan gum to the locust bean gum is from about 1:3 to about 3:1. In such embodiments, the ionizable gel enhancing agent enhances the strength of the cross-linking between the xanthan gum and locust bean gums.

The present invention also provides a method of producing a sustained release solid oral dosage form by e.g., preparing a formulation including a medicament of low aqueous solubility and the sustained release excipient described above.

In certain preferred embodiments, nifedipine is prepared in amorphous form prior to incorporation into the dosage form. Amorphous nifedipine is prepared by solubilizing or dispersing nifedipine crystals in a vehicle, including, e.g., preferably a solid solubilizing agent, prior to incorporation into the formulation.

The present invention is further related to a method of treating a patient by orally administering an oral solid dosage form preferred as set forth above.

In certain preferred embodiments, the mixture of the gelling agent, inert diluent, and ionizable gel strength enhancing agent are optionally granulated with a dispersion or solution of a pharmaceutically acceptable hydrophobic material in an amount sufficient to slow the

hydration of the gelling agent without disrupting the gel matrix thus formed.

While the medicament can be any drug with a solubility of less than 10 g/l in aqueous solution, in a particularly preferred embodiment, the medicament comprises a therapeutically effective dihydropyridine, such as e.g., nifedipine that is prepared in amorphous form, e.g., as amorphous particles.

By "sustained release" it is meant for purposes of the present invention that the therapeutically active medicament is released from the formulation at a controlled rate such that therapeutically beneficial blood levels (but below toxic levels) of the medicament are maintained over an extended period of time ranging from e.g., about 12 to about 24 hours, thus, providing, for example, a 12 hour or a 24 hour dosage form.

By "bioavailable" it is meant for purposes of the present invention that the therapeutically active medicament is released from the sustained release formulation and becomes available in the body at the intended site of drug action.

By "poorly soluble", it is meant that the therapeutically active medicament has an aqueous solubility of less than about 1000 milligrams per liter (mg/l).

By "moderately soluble", it is meant that the therapeutically active medicament has an aqueous solubility of less than about 10 grams per liter (g/l).

The term "environmental fluid" is meant for purposes of the present invention to encompass, e.g., an aqueous solution, or gastrointestinal fluid or, in-vitro, dissolution media used for, e.g., confirmation of the dissolution properties of the formulation..

By "increasing the gel strength", it is meant that the ionizable gel strength enhancing agent interacts with the gelling agent used in the sustained release excipient in such a manner as to desirably prolong the release of drug from the formulation when the formulation is exposed to, e.g., gastrointestinal fluid, and further it is meant that the hydration of the gel and the gel strength provide a desired release rate of drug from the dosage without, for example allowing a phenomena known as dose-dumping.

By the term "dose-dumping" it is meant that the dosage form undesirably releases too much of the drug into the environmental fluid at too early a time after exposure into the environmental fluid. In other words, the dosage-form would thereby not be capable of providing the desired sustained release and sustained effect in-vivo.

DETAILED DISCLOSURE OF THE INVENTION

In the present invention, it has been determined that the gelling agent may be comprised of materials suitable for providing a controlled release gel when exposed to environmental fluids according to the invention. It has been found that a sustained release excipient comprising only a gelling agent (e.g. a hydrophilic gum) may not be sufficient to provide a suitable sustained release of an insoluble medicament to provide a 24 hour formulation, nor to prevent an initial "burst" (i.e., dose dumping) of drug release from the formulation when the formulation is exposed to a fluid in an environment of use, e.g. an aqueous solution or gastrointestinal fluid. This is especially the case with certain medicaments such as those which are only moderately soluble, and is especially true with drugs such as nifedipine which are only poorly soluble.

In a most preferred embodiment the gelling agent comprises a mixture of a xanthan gum and a locust bean gum capable of cross-linking with the xanthan gum when the gums are exposed to an environmental fluid. In this most preferred embodiment the ionizable gel enhancing agent acts to enhance the strength of cross-linking between the xanthan gum and the locust bean gum and thereby prolong the release of the medicament component of the formulation.

Acceptable gelling agents which may also be used, in addition to xanthan gum and locust bean gum, in the present invention include those gelling agents well-known in the art. Examples include naturally occurring or modified naturally occurring gums such as alginates, carrageenan, pectin, guar gum, modified starch, hydroxypropylmethylcellulose, methylcellulose, and other cellulosic materials or polymers, such as sodium carboxymethylcellulose and hydroxypropyl cellulose and mixtures of the foregoing. This list is not meant to be exclusive.

Xanthan gum is a high molecular weight ($>10^6$) heteropolysaccharide. Other preferred heteropolysaccharides include derivatives of xanthan gum, such as deacylated xanthan gum, the carboxymethyl ether, and the polyethylene glycol ester that may be readily substituted for xanthan gum.

The controlled release properties of the formulations of the present invention may be optimized when the ratio of xanthan gum to locust bean gum is about 1:1, although xanthan